Bursts as a unit of neural information: 
making unreliable synapses reliable

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Several lines of evidence indicate that brief (<25 ms) bursts of high-frequency firing have special importance in brain function. Recent work shows that many central synapses are surprisingly unreliable at signaling the arrival of single presynaptic action potentials to the postsynaptic neuron. However, bursts are reliably signaled because transmitter release is facilitated. Thus, these synapses can be viewed as filters that transmit bursts, but filter out single spikes. Bursts appear to have a special role in synaptic plasticity and information processing. In the hippocampus, a single burst can produce long-term synaptic modifications. In brain structures whose computational role is known, action potentials that arrive in bursts provide more precise information than action potentials that arrive singly. These results, and the requirement for multiple inputs to fire a cell suggest that the best stimulus for exciting a cell (that is, a neural code) is coincident bursts.

can only act if the channels are opened first by neurotransmitter. When synapses are stimulated repeatedly (Fig. 2), the higher the probability of transmitter release at a given synapse, the faster the NMDA channels at that synapse will become blocked. In experiments performed on hippocampal CA1 synapses, a presynaptic stimulus strong enough to activate many synapses was given repetitively. The key observation was that the response mediated by NMDA channels was gradually reduced with at least two very different time constants. The fast time constant is taken to reflect a small population of synapses with a high P in the range of 0.3-0.5; the slow time constant suggests that the remaining synapses (0.75%) have a much lower P, in the range of 0.06-0.09.

Another line of evidence for unreliable synapses comes from measuring the excitatory postsynaptic current (EPSC) elicited by excitation of single pre-synaptic axons. Study of such 'unitary' responses shows a probability of successful transmission of less than one. As it is known that a unitary connection can sometimes be due to multiple sites of synaptic contact, the probabilities established in this way are usually an upper limit. In three heroic experiments, anatomical methods were used to establish that the synaptic connection between a CA1 pyramidal cell and an interneuron was due to a single synapse. Dual recordings from these three pairs of neurons determined probabilities of transmission of 0.35, 0.85 and 0.95.

It is now becoming possible to determine P at individual synapses by optical methods. For example, using a confocal microscope it is possible to observe individual spines of CA1 pyramidal cells in a slice preparation. Brief Ca2+ elevations in individual spines occur probabilistically in response to single presynaptic stimuli. These signals are due to Ca2+ entry through the NMDA channels near resting potential. At the large mushroom spines that are typically studied, the probability that presynaptic stimulation will elicit a postsynaptic signal is 0.02, but sites with even lower P have been detected by optical methods (see below).

It is worth emphasizing that a low P synapse is not the same as a 'silent synapse'. These are defined by their absence of functional AMPA channels, but could conceivably have a high P, as detected by NMDA channels. There has been some concern that the unreliable nature of synaptic transmission might arise from unreliable stimulation of the axon or failure of action potentials to propagate to release sites. However, direct investigation of these possibilities suggests that these are not major sources of unreliability.

**Bursts are reliably transmitted by unreliable synapses**

Although synapses might have a low P during single stimuli, bursts of stimuli can cause presynaptic facilitation that increases P and makes it highly probable that transmission will occur at some point during the burst. Facilitation of excitatory responses has been demonstrated using responses that are the summation of many synaptic inputs. By simply giving two presynaptic stimuli in close temporal proximity, it can be seen that the second response is usually larger than the first (paired-pulse facilitation). An example of facilitation for a burst of four stimuli is given below. Facilitation occurs because the intracellular Ca2+ elevation and Ca2+ binding caused by the initial stimulus has not returned to baseline before the second stimulus (Fig. 2).

Most experiments on facilitation have measured averages over a population of synapses, but a recent study provides a description of facilitation at single hippocampal CA1 synapses. The synapse was stimulated with pairs of closely spaced stimuli. The postsynaptic response to the first stimulus occurred probabilistically as expected. The real surprise is that the response to the second stimulus depended strongly on what happened during the first. If release did not occur on the first, the conditional probability of release on the second was over 0.9 irrespective of the value of P (Fig. 3A), indicating strong facilitation. If release did occur on the first, the probability of a second release was below 0.1 when measured 6 ms later (Fig. 3B, squares), indicating depression. Recovery from this depression occurred in about 15 ms. This shows that facilitation is even stronger than expected from the study of the responses generated by populations of synapses, which are influenced by a combination of facilitation and depression processes. It also shows that facilitation is so strong that a burst of only two action potentials will produce successful synaptic transmission at almost every synapse.

The study of synapses with optical methods provides a second line of evidence that transmission during a burst becomes reliable, even for very low P synapses.
Transmission at a low ability if there was no release in response to the first pulse. A function of time, if there was release in response to the first pulse. Open circles show the probability of depression.

Successful release produces a subsequent depression of release that lasts more than 20 ms after the first pulse, the success probability for the second stimulus was computed only for trials where there was no release on the first in order to avoid the confounding effects of depression. (B) Successful release produces a subsequent depression of release that lasts about 20 ms. Closed squares show the probability of release in response to the second pulse as a function of time, if there was release in response to the first pulse.

Open circles show the probability if there was no release in response to the first pulse. (C) Optical methods show reliable transmission at a low P synapse during a burst. Transmission was detected by a very local rise in Ca\(^{2+}\) produced by Ca\(^{2+}\) entry through the NMDA channel. The postsynaptic voltage was held at -15 mV to relieve the Mg\(^{2+}\) block. Thus, NMDA channels opened and allowed Ca\(^{2+}\) entry whenever a vesicle was released from the presynaptic terminal. Two sites of synaptic transmission with different properties were detected. At site A, transmission occurred during a burst of ten presynaptic stimuli irrespective of whether the frequency of stimulation was 2 Hz or 20 Hz. At site B, transmission never occurred at 2 Hz in four groups of ten stimuli (only one group is shown). When facilitation was caused by giving the ten stimuli in a burst at 20 Hz, all four of the bursts caused transmission (only one is shown). Vertical scale bar, 15% change in Ca\(^{2+}\) fluorescence (F/F). Horizontal scale bar, 5 s.

This graph shows that a second stimulus immediately following the first is likely to produce depression that lasts several hundred milliseconds. Open circles show the probability of depression on the second stimulus as a function of time, if there was release in response to the first pulse. Closed squares show the probability of release on the first pulse as a function of time, if there was no release in response to the first pulse.

Fig. 3. Demonstration that the facilitation that occurs during a burst makes information transfer reliable. Data is from single CA1 hippocampal synapses. (A) This graph shows that the probability of successful release in response to a second pulse in a pair is very high (~0.9). The data is presented for 16 cells that had differing release probabilities in response to the first pulse, as plotted on the x-axis. In those experiments in which the second pulse was given less than 20 ms after the first pulse, the success probability for the second stimulus was computed only for trials where there was no release on the first in order to avoid the confounding effects of depression. (B) Successful release produces a subsequent depression of release that lasts about 20 ms. Closed squares show the probability of release in response to the second pulse as a function of time, if there was release in response to the first pulse. Open circles show the probability if there was no release in response to the first pulse. (C) Optical methods show reliable transmission at a low P synapse during a burst. Transmission was detected by a very local rise in Ca\(^{2+}\) produced by Ca\(^{2+}\) entry through the NMDA channel. The postsynaptic voltage was held at -15 mV to relieve the Mg\(^{2+}\) block. Thus, NMDA channels opened and allowed Ca\(^{2+}\) entry whenever a vesicle was released from the presynaptic terminal. Two sites of synaptic transmission with different properties were detected. At site A, transmission occurred during a burst of ten presynaptic stimuli irrespective of whether the frequency of stimulation was 2 Hz or 20 Hz. At site B, transmission never occurred at 2 Hz in four groups of ten stimuli (only one group is shown). When facilitation was caused by giving the ten stimuli in a burst at 20 Hz, all four of the bursts caused transmission (only one is shown). Vertical scale bar, 15% change in Ca\(^{2+}\) fluorescence (F/F). Horizontal scale bar, 5 s.

A second vesicle is released, the response it produces will be attenuated. This is because the transmitter released by the first vesicle binds to nearly all of the postsynaptic AMPA channels, resulting in many of them entering the desensitized state\(^{52,53}\). For reviews of saturation and desensitization processes, see Refs 52,53). Synaptic properties might thus serve to produce a virtually deterministic response to a burst (ignoring the jitter related to which one of the spikes in the burst actually produces transmission). If such perfection were achieved, the only determinant of the postsynaptic response to a burst would be the postsynaptic responsiveness of AMPA channels (described by the quantum-size parameter, q).

Quantal size is precisely the quantity that, according to some views\(^{14}\), is the only synaptic property modulated by long-term potentiation (LTP), the best current model of memory storage. Even if one supposes that P is also modulated by LTP, the effect of P on the postsynaptic response to a burst would be small and perhaps negligible, as argued above. Thus, it appears that synaptic physiology might have evolved to store memory by a postsynaptic modification that can be reproducibly read out by a single burst.

**Single bursts can induce synaptic modification**

The importance of bursts as a functional unit of information is supported by the finding that single bursts are sufficient to produce LTP and long-term depression (LTD)\(^{15}\). Most of the work performed on LTP and LTD in the hippocampal slice has been done in the absence of cholinergic modulation, and under these conditions hundreds of action potentials are typically required to produce synaptic modification. Single bursts are ineffective in this situation. However, the hippocampal-slice condition is not a good model for the in vivo awake state; in making the slice, all neuromodulatory inputs have been severed. During normal brain function, cholinergic input to the hippocampus plays an important role in inducing a 5–8 Hz network oscillation called theta rhythm. A network oscillation of the same frequency can be induced in the slice by the application of the acetylcholine agonist, carbamol. In this oscillatory state, synaptic plasticity is enhanced greatly\(^{16}\). Indeed, it becomes so enhanced that a single brief (15 ms) burst can produce long-term synaptic modifications\(^{16}\). Figure 4A shows that a single burst applied at the peak of the theta oscillation induces LTP. It was also shown that a single burst applied at the trough produces LTD (de-potentiation) of previously potentiated synapses. Bursts with only two action potentials produce little synaptic modification; bursts with three action potentials produce some LTD or LTP; and bursts with four action potentials produce nearly maximal LTD or LTP (note that during cholinergic modulation, P is lower than is shown in Fig. 3A). It thus appears that during the appropriate neuromodulatory conditions, the processes of synaptic modification are very sensitive to the types of bursts that occur in vivo.

**Bursts are informationally rich; in some brain regions single spikes might be noise**

If bursts are important units of information, it should be possible to demonstrate that they are information-rich in cases where one knows the computation being performed. The results from several
different brain regions bear on this question. In the hippocampus, cells use polymodal input to compute the animal’s location (place) in a given environment. This is measured experimentally by mapping the position of the animal when a spike occurs. Figure 5A shows that the resulting place-field is defined more accurately when only bursts are considered than when all spikes are considered (see also Ref. 59). This indicates that downstream neurons would get a better indication of the animal’s position if single spikes were filtered out and the neurons were excited only by bursts.

The second brain region where relevant data has been obtained is primary visual cortex. Cells in this region compute the orientation and spatial frequency of stimuli. Figure 5B (Ref. 60) shows that presentation of visual stimuli increased both the rate of single spikes and the rate of bursts. Under these conditions, the rate of bursts depended strongly on orientation. By contrast, the rate of single spikes had almost no dependence on orientation. Similar results were found for spatial-frequency selectivity (see also Ref. 61). This suggests that single spikes are not just a weaker version of the computation that is being performed, but are actual noise (disinformation). It follows that the ability of synapses to not transmit single spikes might be a crucial form of filtering. Indeed, given that neurons fire spontaneously, a way of filtering out such noise without compromising the detection of bursts of meaningful information makes good sense.

Very recent work from Livingstone et al. provides dramatic further evidence for the importance of bursts in primary visual cortex. Each spike recorded from alert, freely viewing monkeys could be assigned a location in the visual field since eye position was measured directly. Surprisingly, plots of all spikes (Fig. 6A) show little if any indication of an object. However, if only bursts are plotted (Fig. 6B), the location and
orientation of the object can be easily discerned. This experiment demonstrates directly that bursts are very infrequent in the absence of an appropriate visual stimulus.

Another computation performed by the brain is the determination of motion direction in the area MT. Here the importance of bursts is less clear. Analysis of spike trains was used to estimate the direction of coherent motion in an array of spots, some fraction of which were moving in the same direction. Near threshold, it takes the animals several seconds to detect the coherent motion, and it is therefore legitimate to analyze spike trains over several seconds. The results show that if bursts are treated as single events, a better estimate of direction can be made. However, if only bursts are considered, there is a marginally poorer estimate. In this case it is clear that single spikes are simply noise might be true under certain circumstances, but cannot be considered a valid generalization.

A final example is the bursts that are generated by visual stimulation in the lateral geniculate nucleus. This structure operates in a burst mode and a non-burst mode, depending on which neuromodulators are present. When bursts are generated, they enhance the detection of dim stimuli.

A neural code: coincident bursts

Bursts will successfully produce transmission at a synapse, but the IPSP generated by a single synapse is 1/15 to 1/30 of the depolarization required to reach threshold in hippocampal pyramidal cells and 1/400 in hippocampal granule cells. Single axons often make multiple synapses with their target neuron but, with a few exceptions, their co-ordinated action is still too small to trigger a spike. Thus, for most neurons, it will take the summation of ‘coincident inputs’ from multiple axons to trigger a postsynaptic response. The smallest number of active inputs required to fire the postsynaptic cell will occur if these inputs are firing bursts. It therefore seems likely that one form of neural coding is coincident bursts.

The degree of coincidence required to fire the postsynaptic neuron efficiently will depend on the temporal integration properties of the neuron (for a review, see Ref. 9). It is tempting to equate this integration time with the passive time constant of the postsynaptic neuron, but it now appears that temporal integration is a more-complex process dependent on many postsynaptic processes. In cortical neurons it is affected strongly by the voltage-dependent conductances. In other cases, the period of temporal integration might be lengthened to the 100 ms range by plateau potentials or long-lived synaptic conductances, such as the NMDA conductance. In yet other cases, specializations exist to bring the period of integration down to the millisecond range. It thus seems likely that the period of temporal integration has to be determined on a case-by-case basis.

An important perspective on the role of bursts and temporal coincidence comes from consideration of the gamma (40 Hz) oscillations found in cortex and hippocampus. It has been proposed that these oscillations play a role in ‘binding’ together different parts of a given perceptual item. The group of cells whose firing represents an item will fire synchronously and can therefore be recognized by other neurons using coincidence detection. It has been unclear, however, what the meaning of synchronicity is in this context. If multiple items must be represented, are they represented by groups that fire synchronously at different phases of a 40 Hz cycle (in which case synchronicity must occur at the millisecond scale)? Alternatively, are different items represented by groups that fire on successive gamma cycles (in which case synchronicity in the 10 ms range would suffice)? Recent theoretical and experimental work supports the latter model, at least in the context of memory processes. In particular, the assumption that memory sequences are read out from the hippocampal CA3 region at one memory per gamma cycle provides a quantitative description of the phase-advance of hippocampal place-cell firing as a rat traverses a familiar linear track.

This kind of temporal organization of memory read-out is compatible with communication of information by bursts. The duration of a burst (<25 ms) (Fig. 1) produces a temporal smear. However, this smear is not problematic if the functional definition of synchronicity is that cells fire in the same gamma cycle, the duration of which is 25–30 ms.

Concluding remarks

The fact that stereotyped bursts occur, are information-rich, and are reliably transmitted to postsynaptic targets suggests that bursts have a special role in neural signaling. The best input for firing a cell (that is, a neural code) will be coincident bursts. If bursts are the signal and single spikes are noise, as appears to be true in some cases, then our view of the ‘unreliable synapse’ flips in an interesting way. The synapse is reliable in transmitting the signal, what is unreliable is its failure to filter out all the noise. The perfect synapse would never produce a response to a single presynaptic spike (have a P of zero), yet it would always transmit during a burst (that is, have infinite facilitation). Interestingly, manipulations that reduce P, such as some neuromodulators, enhance facilitation and so might help the synapse to approach perfection.

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